# The Bromination of Methoxyaromatic Ketones. An Interpretation of Substituent Interactions

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The rates of ring bromination of 11 variously substituted methoxyaromatic ketones are reported. The data are discussed with respect to the net substituent effect (represented by $\Sigma\sigma^+$) as modified by substituent interaction (represented by $\Sigma\sigma_i^+\sigma_j^+$) using the following equation, $\log (k/k_0) = p\Sigma\sigma^+ + q\Sigma\sigma_i^+\sigma_j^+$, where $p$ and $q$ describe the sensitivity of the reaction to the net substituent effect and substituent interaction, respectively. For compounds bearing the methoxy and propionyl groups ortho to each other the results are consistent with a steric inhibition to substituent interaction. This steric inhibition is evoked quantitatively in terms of the above equation. The treatment shows that electrophilic attack by bromine is itself insensitive to steric effects; these latter make their appearance *via* substituent interaction.

A recent publication[1] from these laboratories treated the bromination of polysubstituted benzenes in terms of both the inherent contribution of each substituent on reactivity (using $\Sigma\sigma^+$) and the influence of substituent interactions, as measured by the term $\Sigma\sigma_i^+\sigma_j^+$. The compounds used in this prior study were selected so as to avoid certain complications, such as the presence of very bulky groups, groups whose substituent action is orientation dependent, etc., which might conceivably be faced after the fundamental soundness of the approach was demonstrated. The provocative nature of the results obtained leads us at this time to a consideration of the bromination of aromatic ketones bearing a methoxy substituent in the aromatic ring. A study of the influence of the keto group on reactivity was our motivation for this work; the presence of the methoxy group was necessary to activate the ring towards electrophilic substitution, without which the keto–enol system might undergo bromination as well. As we shall see, this precaution ensures a sufficiently superior reactivity of the aromatic moiety over the keto moiety such that the latter may be disregarded as a reaction center and viewed as a substituent.

## Results

For purposes of product analysis three compounds were chosen—*p*-methoxyacetophenone, *o*-methoxyacetophenone, and 4,5-dimethyl-2-methoxypropiophenone. Following a procedure given in the Experimental Section, each was brominated and gave rise to a single product along with a trace of starting material. An nmr analysis of these products revealed that only ring bromination had occurred. These data are given in Table I.

The rate data were obtained by the method of automated couloamperometry as previously described.[2,3] The kinetic characterization of the system was carried out in three series of rate studies allowing, in each instance, one factor among acidity, ketone concentration, and bromine concentration to vary. The ionic strength was controlled by the addition of NaBr. Table II shows these results, which demonstrate that the reaction rate is independent of acid concentration and first order in both bromine and ketone concentrations. The kinetic behavior is then adequately represented by eq 1. It is worth noting that an expression

$$\frac{-d[Br_2]}{dt} = k[Br_2][\text{ketone}] \qquad (1)$$

of the same form as eq 1 could be obtained for the bromination of the keto moiety if the bromination of its enol form were rate determining.[4,5] Thus the absence of a kinetic dependence on acidity does not constitute a criterion for deciding which part of the molecule reacts; product studies are necessary to clarify this point.

In all, the bromination rates of 11 variously substituted aromatic ketones were measured under identical conditions of temperature, solvent, and ionic strength. The rate constants are given in Table III, where the position of attack on the ring is noted as well.

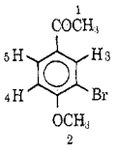
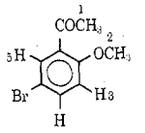
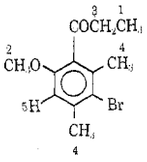
## Discussion

In Figure 1 the values of $\log k$ are plotted against the quantity $\Sigma\sigma^+$.[6] For ease of reference the points are numbered.[7] Two facts are immediately evident: that the points corresponding to bromination para to methoxy correlate well with $\Sigma\sigma^+$ and those (only three in number) corresponding to ortho bromination do not. Compounds **9** and **11**, which are brominated ortho to the methoxy group, represent one difficulty with a treatment of this kind—they are isomers which possess the same value of $\Sigma\sigma^+$ and lead one to expect equivalent rates. This is usually what is found, as demonstrated by the reaction rates of the following three pairs of compounds.

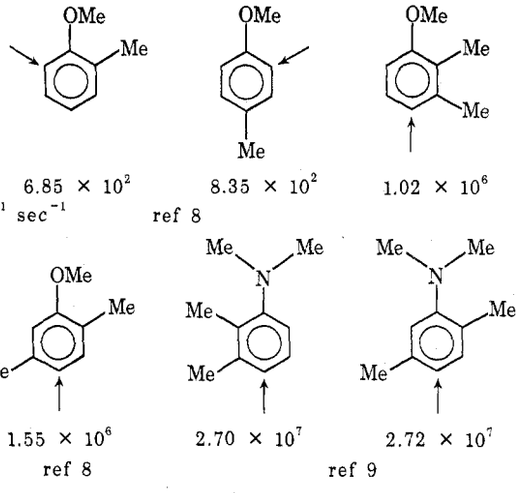
(1) J. E. Dubois, J. J. Aaron, P. Alcais, J. P. Doucet, F. Rothenberg, and R. Uzan, *J. Amer. Chem. Soc.*, **94**, 6823 (1972), and references cited therein.
(2) J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964).
(3) J. E. Dubois and J. J. Aaron, *J. Chim. Phys.*, **66**, 1109 (1969).
(4) R. P. Bell and G. C. Davies, *J. Chem. Soc.*, 902 (1964).
(5) J. E. Dubois and J. Toullec, *J. Chim. Phys.*, **65**, 2166 (1968); *Chem. Commun.*, 212 (1969).
(6) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).
(7) (a) The value of $\sigma_0^+$ for the groups RCO– is unknown. We have used the $\sigma_M$ value of $CH_3CO$– (0.376)[7b] for all groups RCO–. Because of the similarity of compounds **1**, **3**, and **5** and **2**, **4**, and **6** we consider only compounds **3** and **4** in the figures and tables presented. (b) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 173.

TABLE I

NMR SPECTRA OF SOME BROMINATED METHOXYAROMATIC KETONES

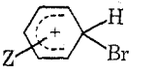
| Registry no. | Brominated ketone | Chemical shift, δ, ppm[a] δ1 | δ2 | δ3 | δ4 | δ5 |
|---|---|---|---|---|---|---|
| 35310-75-9 |  | 2.53 | 4.04 | 8.02 | 7.20 | 8.22 |
| 16740-73-1 |  | 2.53 | 3.90 | 6.82 | 7.47 | 7.72 |
| 36871-61-1 |  | 1.10 | 3.75 | 2.61 | 2.19<br>2.38 | 6.61 |

[a] In $CCl_4$ solution, with tetramethylsilane as reference.




In the present instance this is not true, which causes one to seek some special effect which alters preferentially the reactivity of one of the isomers; this point will be considered later.

We would like to discuss these results in terms of a previous analysis from these laboratories[1] which concerned the correlation of bromination rates of a large population (44 polymethylated benzenes, substituted anisoles, and *N*,*N*-dimethylanilines) of mono- and polysubstituted benzenes. In this prior study the reaction mechanism for all compound was assumed to be identical (arguments were presented to show that this may be so), *i.e.*, all passing through a σ-complex transition state.




The reaction rates within each discrete family of compounds have long been known to correlate with $\Sigma\sigma^+$, yielding a different value of $\rho^+$ in each case.[8,9,10-12]

(8) J. J. Aaron and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 603 (1971).
(9) R. Uzan and J. E. Dubois, *ibid.*, 598 (1971).
(10) F. Rothenberg, P. Alcais, and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 592 (1971).
(11) J. E. Dubois, P. Alcais, and F. Rothenberg, *J. Org. Chem.*, **33**, 439 (1968).
(12) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

TABLE II

REACTION ORDER WITH RESPECT TO THE VARIOUS COMPONENTS

| 2,4-Dimethyl-6-methoxypropiophenone, $M^a \times 10^7$ | $Br_2$, $M^b \times 10^7$ | $k_{obsd}$, $M^{-1}$ sec$^{-1}$ [b] × $10^{-6}$ |
|---|---|---|
| A. Variation of Bromine Concentration | | |
| 6.07 | 0.81 | 1.0 |
| 6.06 | 1.85 | 1.15 |
| 5.70 | 2.84 | 1.2 |
| 8.33 | 5.81 | 1.1 |
| B. Variation of Ketone Concentration | | |
| 4.5 | 2.76 | 1.25 |
| 8.93 | 2.88 | 1.05 |
| 10.80 | 2.49 | 1.0 |
| 12.1 | 2.53 | 1.0 |

C. Variation of Acidity

| Ketone | $HClO_4$, $M$ | $k_{obsd}$,[c] $M^{-1}$ sec$^{-1}$ |
|---|---|---|
| 4-Methoxyacetophenone | 0 | 0.85 ± 8% |
| | 0.10 | 0.79 ± 3% |
| | 0.20 | 0.80 ± 2.5% |
| 4-Methoxypropiophenone | 0 | 0.96 ± 8.5% |
| | 0.10 | 1.06 ± 2% |
| 2,4-Dimethyl-6-methoxy-propiophenone | 0 | 1.64 ± 4% |
| | 0.20 | 1.62 ± 8% |
| | | 1.67 ± 7.5% |

[a] Initial concentration, moles/liter. [b] Electrolyte concentration maintained at 0.10 $M$ by addition of sodium bromide. [c] Total electrolyte concentration maintained at 0.30 $M$ by addition of 0.10 $M$ sodium bromide and sodium perchlorate as required.

A correlation of the entire population was considered by making use of both the term $\Sigma\sigma^+$ and a substituent interaction term of the form $\Sigma\sigma_i{}^+\sigma_j{}^+$, which was assumed to account for specific substituent interactions of an electronic nature. Equation 2 expresses this

$$\log k/k_0 = p\Sigma\sigma^+ + q\Sigma\sigma_i{}^+\sigma_j{}^+ = -11.3\,\sigma^+ - 6.3\,\sigma_i{}^+\sigma_j{}^+ \quad (2)$$
$$r = 0.988 \qquad \Psi = 0.15$$

correlation mathematically, where $k_0$ is the rate of bromination of benzene statistically corrected ($\log k_0 = -5.64$). The quantity $p$ was associated with the $\rho^+$ for the bromination of monosubstituted benzenes

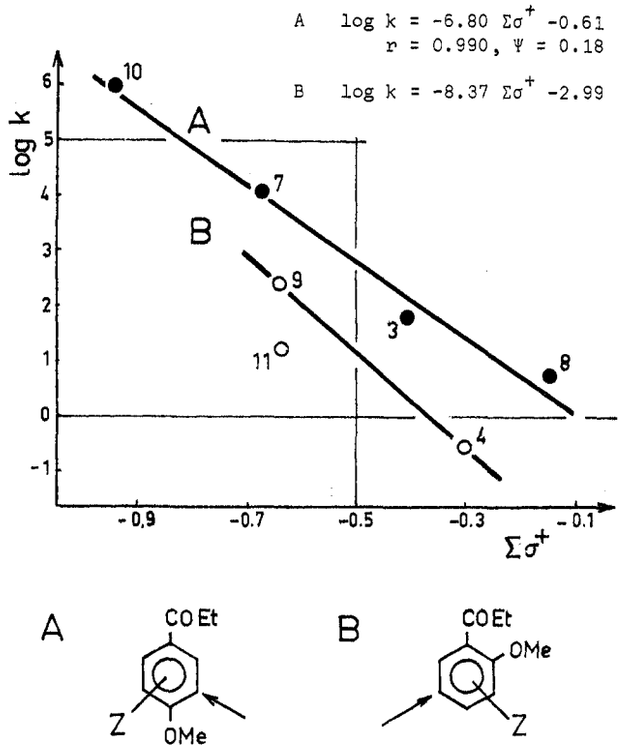



Figure 1.—Correlation of bromination rates with $\Sigma\sigma^+$.

TABLE III
BROMINATION RATES OF SOME METHOXYAROMATIC KETONES IN WATER AT 25.0°[a]

| No. | Ketone | Reaction center[b] | $k_{obsd}$,[c] $M^{-1}$ sec$^{-1}$ × $10^{-3}$ |
|---|---|---|---|
| 1 | 2-Methoxyacetophenone | Para | 0.0605 |
| 2 | 4-Methoxyacetophenone | Ortho | 0.000282 |
| 3 | 2-Methoxypropiophenone | Para | 0.088 |
| 4 | 4-Methoxypropiophenone | Ortho | 0.000375 |
| 5 | 2-Methoxybutyrophenone | Para | 0.089 |
| 6 | 4-Methoxybutyrophenone | Ortho | 0.000362 |
| 7 | 4-Methyl-2-methoxy-propiophenone | Para | 12.9 |
| 8 | 4-Chloro-2-methoxy-propiophenone | Para | 0.00573 |
| 9 | 2,5-Dimethyl-4-methoxy-propiophenone | Ortho | 0.248 |
| 10 | 2,4-Dimethyl-6-methoxy-propiophenone | Para | 1.045 |
| 11 | 4,5-Dimethyl-2-methoxy-propiophenone | Ortho | 0.017 |

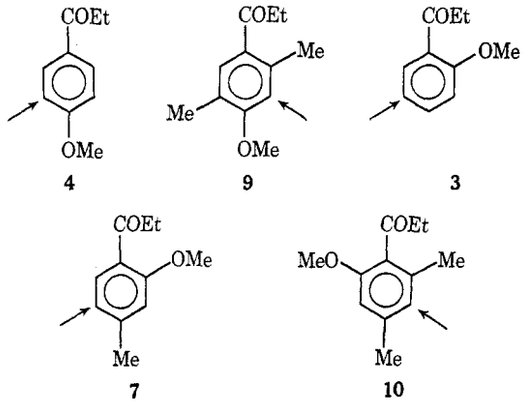
[a] NaBr = 0.10 $M$. [b] The reaction center is designated with respect to the methoxy group. In each case this was verified by vpc product analysis. [c] All rate constants statistically corrected for one reaction center.

(−11.6) and the term $q$ with the sensitivity of the reaction to substituent interaction. The compounds employed in this previous correlation were selected with the hope that they would not exhibit any specific effects other than strictly electronic interactions. Such eventualities as noncoplanarity of rings or steric effects would be difficultly separable from other substituent interactions.

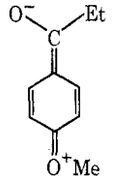
The manifest success of this correlation leads us to question the extent to which the rate constants given in Figure 1 can be estimated by the use of eq 2. The estimated values (log $k_{calcd}$) together with the differences between calculation and experiment (log $k_{exp}$) − log $k_{calcd}$) are given in Table IV. For compounds **4** and **9** the estimated values agree closely with experiment. The well-behaved nature of **9** indicates that the reactivity of its isomer **11** is controlled by features different from those taken into account by the terms $\Sigma\sigma^+$ and $\Sigma\sigma_i^+\sigma_j^+$.

We will come back to this point. This leaves compounds **3**, **7**, **8**, and **10** for consideration.

These four compounds are more reactive than anticipated by the summation of the interaction terms $\sigma_i^+\sigma_j^+$, compound **8** considerably so (2.32 log units) but the others by a quantity nearly equal for all three (≅1 log unit). An explanation of this behavior can be obtained by considering the structures and positions of attack of the predictably reacting compounds **4** and **9** compared with those of the three whose reactivity appears to be augmented over the anticipated value by a constant amount (**3**, **7**, and **10**).




For compounds **4** and **9** an interaction involving the following reasonance form must be important.




The predictability of the reactivity of **4** and **9** indicates strongly that such an interaction is incorporated into the interaction term $\Sigma\sigma_i^+\sigma_j^+$. However, for compounds **3**, **7**, and **10**, which have the keto group and the methoxy group in an ortho arrangement with respect to one another, such a resonance form would be less important for purely steric reasons. If an interaction of this kind is already included in the term $\Sigma\sigma_i^+\sigma_j^+$ the "estimated" reactivity will be necessarily smaller than that found from experiment. For these three compounds, then, what we could be observing is a *steric inhibition of substituent interaction*, pointed out by the application of eq 2. In the case of compound **10**, where the reaction center is flanked by two methyl groups, one is tempted to accord some steric contribution to these groups. This cannot be true, since such compounds fit acceptably into the general correlation (eq 2) along with other polymethyl benzenes which do not have this feature.[10,11]

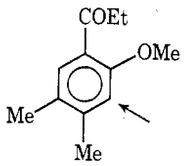
The anomaly mentioned above concerning compounds **9** and **11** also bears on this interpretation. On the assumption that **9** reacts normally, we may inquire

TABLE IV
ESTIMATION OF REACTION RATES USING EQUATION 2

| Compd | Reaction center | $\Sigma\sigma^+$ | $\Sigma\sigma_i^+\sigma_j^+$ | log $k_{exp}$ | log $k_{calcd}$ | log $k_{exp}$ − log $k_{calcd}$ |
|---|---|---|---|---|---|---|
| 3 | Para | −0.402 | −0.292 | 1.944 | 0.80 | 1.14 |
| 4 | Ortho | −0.302 | −0.254 | −0.43 | −0.62 | 0.19 |
| 7 | Para | −0.678 | −0.182 | 4.11 | 3.18 | 0.93 |
| 8 | Para | −0.139 | −0.398 | 0.758 | −1.56 | 2.32 |
| 9 | Ortho | −0.644 | −0.134 | 2.394 | 2.45 | −0.06 |
| 10 | Para | −0.954 | 0.004 | 6.014 | 5.04 | 0.97 |
| 11 | Ortho | −0.644 | −0.134 | 1.230 | 2.48 | −1.28 |
| | | (−0.415)[a] | (−0.125)[a] | | (−0.16)[a] | (1.36)[a] |

[a] Rate estimated using $\sigma^+_{o\text{-MeO}}$; solvolysis −0.445. All other estimates based on $\sigma^+_{o\text{-MeO}}$ −0.678.

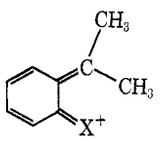
why **11** reacts more slowly than calculated by means of the interaction term $\Sigma\sigma_i^+\sigma_j^+$. Compound **11** is the



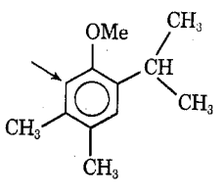

**11**

only one studied involving substitution ortho to methoxy with, at the same time, the keto and methoxy groups ortho to each other.

The large estimated rate may result from an injudicious choice of $\sigma_0^+$ for the methoxy group. The value used for compounds **4** and **9** is that obtained from electrophilic substitution reactions.[13] Another set of $\sigma_0^+$ values exists which have been determined from the solvolysis of ortho-substituted 2-phenyl-2-propyl chlorides.[6] These values are not so large as those determined from electrophilic substitution since resonance structures of the form




are to some extent sterically hindered. The very crowded environment of the methoxy group in compound **11** may inhibit such reasonance, which would make the $\sigma_0^+$ obtained from solvolysis a more valid choice. This value is used for the numbers given in parentheses in Table IV. The calculated rate is, in this case, smaller than the experimental value by 1.36 log units. This deviation is very similar to that found for compounds **3**, **7**, and **10**, where it was suggested that the substituent interaction suffered an attenuation for steric reasons. In compound **11** the keto and methoxy groups are ortho to one another, as they are in compounds **3**, **7**, and **10**. It is therefore suggested that in the case of **11** there are two interactions of steric origin, one of which can be accounted for by a suitable




choice of $\sigma_0^+$ and one of which is similar in nature to that suggested for **3**, **7**, and **10**. The reactivity of 2-isopropyl-4,5-dimethylanisole, considered in a related study,[14] also supports this point of view.

The estimated reactivity (log $k_{calcd}$ = 5.23) is considerably superior to the experimental value (log $k_{exp}$ = 3.516) when one uses the $\sigma^+_{o\text{-MeO}}$ obtained from electrophilic substitution; however, the agreement between calculation and experiment is excellent when the $\sigma_{O\text{-MeO}}$ solvolysis is employed (log $k_{calcd}$ = 3.36). One might be inclined to believe that the low experimental rate is due to a steric effect on the bromination itself, since the reaction center is flanked by both a methyl group and a methoxy group. This interpretation seems unlikely if we consider the reactivity of compound **9** in the present work. In this compound the reaction center is also flanked by a methyl and a methoxy group but the reactivity is quite "normal." It appears that the extremely crowded environment influences the reactivity *via* the methoxy group and not by a direct effect on the reacting center. This line of thought provides a rationale for the anomalous behavior of **11**; to verify this fully more kinetic data for compounds of this kind are needed.

It would appear, then, that the ideas set out in ref 1 are of particular interest in assessing the importance of certain neighboring substituent interactions. The influence of electronic effects seems by and large to be accounted for by the interaction term $\Sigma\sigma_i^+\sigma_j^+$; steric effects appear as systematic deviations from this rule. The data used in ref 1 (except for four compounds possessing the group $-NMe_2$) do not incorporate groups whose electronic interactions would be sterically dependent. In the present case the group RCO– shows, according to its environment, instances of good behavior as well as ill behavior, demonstrated by the application of eq 2. This, we feel, indicates the utility of this approach in helping to disentangle the manifold complexities of substituent effects on the electrophilic substitution of polysubstituted benzenes.

## Experimental Section

**Materials.**—All methoxyaromatic ketones were prepared by the reaction of the parent hydroxyaromatic ketones with dimethyl sulfate in methanolic sodium hydroxide.[15] The hydroxyaromatic ketones were synthesized by the Fries reaction, as previously described.[15,16] The data for three substituted methoxypropiophenones, not previously recorded, are now reported.

(13) C. W. MacGary, Y. Okamoto, and H. C. Brown, *J. Amer. Chem. Soc.*, **77**, 3037 (1955).

(14) J. E. Dubois and D. Balou, unpublished results.

(15) F. Krausz, R. Martin, and J. P. Gavard, *Bull. Soc. Chim. Fr.*, 640 (1966).

(16) F. Krausz and R. Martin, *ibid.*, 2192 (1965).

4-Methyl-2-methoxypropiophenone had ir ($CH_2Cl_2$, 5%) 1669 (C=O), 1610, 1570, 1495, 1460 (aryl C=C), and 1209 $cm^{-1}$ (CO).

*Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.58; H, 7.80.

2,5-Dimethyl-4-methoxypropiophenone had ir ($CH_2Cl_2$, 5%) 1672 (C=O), 1610, 1560, 1508, 1462 (aryl C=C), and 1231 $cm^{-1}$ (CO).

*Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.94; H, 8.39. Found: C, 74.34; H, 8.42.

4-Chloro-2-methoxypropiophenone had ir ($CH_2Cl_2$, 5%) 1673 (C=O), 1590, 1568, 1480, 1460 (aryl C=C), and 1241 $cm^{-1}$ (CO).

*Anal.* Calcd for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58; Cl, 17.85. Found: C, 60.11; H, 5.56; Cl, 17.74.

All inorganic compounds used (perchloric acid, sodium perchlorate, sodium bromide, bromine) were reagent grade. Water used as solvent was distilled twice over alkaline potassium permanganate.

**Kinetic Measurements.**—All kinetic measurements were performed by the automatic method of couloamperometry as previously described.[2,3]

**Synthesis of Reaction Products.**—The same method was used for the preparation of the three bromo ketones (3-bromo-4-methoxyacetophenone, 5-bromo-2-methoxyacetophenone, 3-bromo-2,4-dimethyl-6-methoxypropiophenone).

To a mechanically stirred solution of 4.5–4.9 g (0.025 mol) of methoxyaromatic ketone in 250 ml of acetic acid, a solution of 4.0 g (0.025 mol) of bromine in 50 ml of acetic acid was added in small portions. After complete addition of bromine (40 min), about 50 ml of water was added to accelerate the reaction; the mixture was stirred for 2 hr. It was extracted three times with carbon tetrachloride and dried over sodium carbonate. Most of the $CCl_4$ was evaporated. The $CCl_4$ concentrated layer was analyzed and its components were separated by preparative gas chromatography. The following columns were used: 20% XF-1150 and 10% UCON Polar on Chromosorb W (Aerograph Co.). Vpc analysis showed traces of the starting methoxy aromatic ketone and in each case only one brominated compound, identified by nmr as the nuclear bromo ketone (see Table I). The retention times of these synthesized bromo ketones were found to be identical with those of the bromo ketones obtained under kinetic conditions.

**Registry No.**—**1**, 579-74-8; **2**, 100-06-1; **3**, 5561-92-2; **4**, 121-97-1; **5**, 13404-83-6; **6**, 4160-51-4; **7**, 36871-54-2; **8**, 36871-55-3; **9**, 36871-56-4; **10**, 5384-14-5; **11**, 36871-58-6.

# Cyclopropylamines as Intermediates in a New Method for Alkylation of Aldehydes and Ketones

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A series of 1-(N,N-disubstituted amino)bicyclo[*n*.1.0]alkanes was prepared from cyclic ketone enamine derivatives and methylene or ethylene iodide and diethylzinc or diazomethane or diazoethane and cuprous chloride. Thermal opening in aqueous methanol furnished the $\alpha$-alkylated and ring-expanded ketones. Similarly, propionaldehyde was converted to isobutyraldehyde (49%), cholestenone to 4-methylcholestenone (76%), and 17-$\beta$-hydroxy-5-$\alpha$-androstan-3-one to 2$\beta$-methyl-17$\beta$-hydroxy-5$\alpha$-androstan-3-one (67%) through cyclopropylamine intermediates. The thermolysis is accelerated by surface-active agents, *i.e.*, 10% Pd/C. Opening of the cyclopropylamines in the presence of acrylonitrile gave products corresponding to those obtained with the alkylated enamines. Hydrogenolyses of some bicyclic cyclopropylamines furnished *N*-(2-methylcycloalkyl)amines.

In syntheses of aliphatic compounds, the $\alpha$-alkylation of ketones and aldehydes is the most widely used reaction principle for carbon to carbon bond formation. Classically, such alkylations are accomplished by formation of enolate anions or enols and reactions of these with electrophilic alkylating agents. In order to overcome some of the difficulties inherent in enolate anion generation and alkylation and to achieve controlled monoalkylation, regiospecificity, and stereospecificity, considerable effort has been spent during the past decades on the development of new alkylation methods. The Stork enamine alkylation principle[1] was notably most stimulating[2] and useful[3] to synthetic chemists.

Our present report describes the formation and use of cyclopropylamines as intermediates in the $\alpha$-alkylation of ketones and aldehydes. The advantages of this new synthetic principle are (a) selective formation and isolation of pure monoalkylation products; (b) regiospecificity in positioning of new substituents; (c) improved alkylation yields in some of the studied examples where reported yields obtained by other methods were found to be low.

This new alkylation route formally parallels the recently developed use of cyclopropyl ethers as alkylation intermediates.[4,5] However, in contrast to that reaction sequence it is now possible to avoid drastic acidic treatment and to achieve cleavage of the cyclopropane intermediates under neutral conditions.

**Formation of Cyclopropylamines.**—The most practical method for large-scale preparations of tertiary cyclopropylamines from carbonyl compound precursors was found to be the reaction of diethylzinc and diiodomethane[6,7] with enamines. For small-scale preparations the alternative method of diazomethane–cuprous chloride[8] induced addition of methylene to enamine double bonds was more satisfactory. Analo-

(1) G. Stork, R. Terrell, and J. Szmuszkovics, *J. Amer. Chem. Soc.*, **76**, 2029 (1954).

(2) For a summary of enamine chemistry with 731 references see M. E. Kuehne in "Enamines: Their Synthesis, Structure an Reactions," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969.

(3) A summary of enamine applications to syntheses of natural products is M. E. Kuehne, *Synthesis*, 510 (1970).

(4) E. Wenkert and D. A. Benges, *J. Amer. Chem. Soc.*, **89**, 2507 (1967).

(5) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *ibid.*, **92**, 7428 (1970).

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